



The Importance of Clinical Trials for Natural Products

The Wake Forest and Brigham and Women's Center for Botanical Lipids



Future of Dietary Supplements

YESTERDAY:

- High Growth
- Cluttered Category
- Short Life Cycle
- Weak Brands
- Fragmented Category

Unproven
Dietary Supplements

TODAY:

- Growth Slowed
- Category Regrouping
- Skepticism-HCP/Consumer
- Regulatory Involvement
- Untapped Demand

THE FUTURE:

- Science-Based, Ethical Products
- Strong IP
- Long Life Cycles
- Strong, Power Brands
- HCP Involvement
 - Development
 - Marketing
- Sophisticated, Ethical Marketing

Mechanistically Based/Clinically
Proven Dietary Supplements,
Medical Foods and Botanical
Rx Products

Why Do Clinical Trials?

- It is the right thing to do. When we provide products to humans, there is a moral and ethical responsibility that they be both safe and effective
- Rigorous clinical trials are critical if we are to move this industry to the next level, and enhance our credibility with our patients and their physicians
- Clinical trials will dramatically increase the profitability of those companies that are progressive enough to lead (ex. supplementation of infant formula for cognitive development)

How Will It Make You More Profitable?

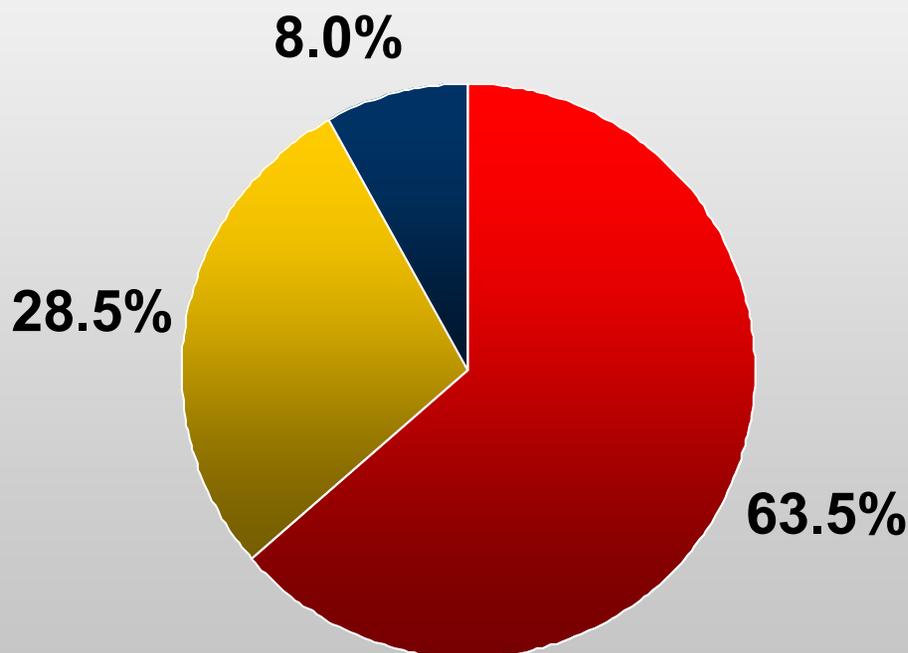
Major Barriers to Entry

(your competitive edge)

- Intellectual property
- Control of the supply chain
- Rigorous clinical trials to support the safety and efficacy of the product and its regulatory status
- Sophisticated, ethical marketing including physician, naturopaths, pharmacist and consumer detailing.

Physicians Are Overwhelmingly Positive If Natural Products are Taken Through Reasonable Safety and Efficacy Trials

(detailed interviews with 203 MDs)

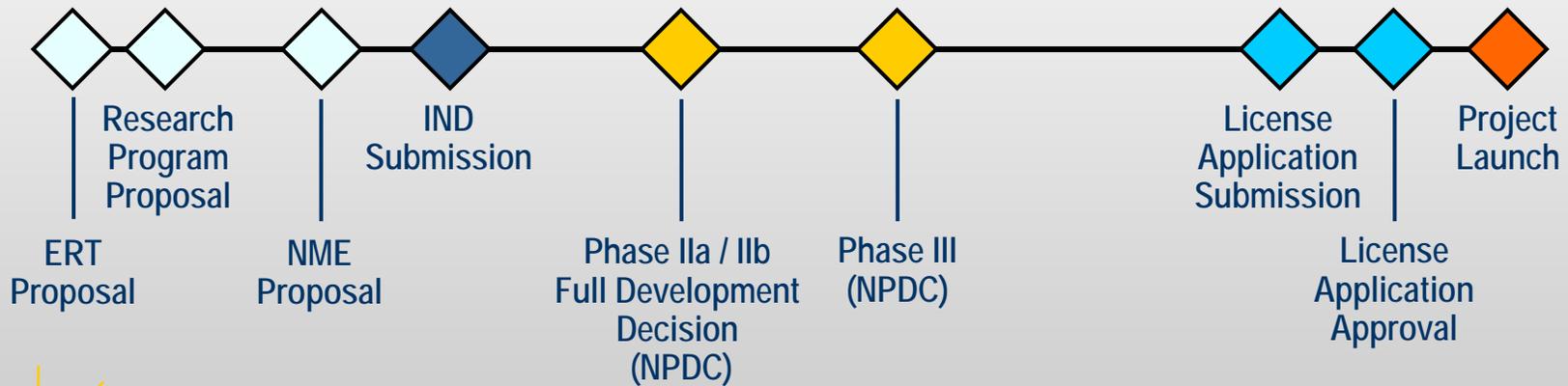


- Recommend as Useful
- Neither Recommend Nor Discourage
- Not Recommend

What are Clinical Trials? Clinical trials are designed to test **safety and effectiveness in humans. They take place in phases. In each phase, different research questions are answered**

- **Phase I:** What is the safe dose? How does the treatment affect the human body? How should the treatment be given?
- **Phase II:** Does the treatment treat the disease or cure the condition?
- **Phase III:** Is the treatment better than, the same as, or worse than the standard (or most widely accepted) treatment? If there is no standard treatment available, is it better than, the same as, or worse than a placebo?

R&D Process Milestones for Drugs



ERT=Experimental Research Target
NME=New Molecular Entity
IND= Investigational Drug

The Bad News

Researchers at Tufts University found that new medicines cost an average of \$802 million to bring to market.

Tufts Center for the Study of Drug Development
November 30, 2001

THE PROBLEM: We have all agreed that we have a moral and ethical responsibility that our products be both safe and effective. I have also shown you that it costs over \$800 million over 8 years to develop an ethical drug. You tell me that the margins of natural products simply will not support that type of development. What are we to do?

Can We Reduce the Cost and
Time that It Takes to Develop an
Ethical, Natural Product?

Key Questions to Ask When Designing Clinical Trials for a Natural Product

- Is there a **strong theoretical basis and some data to suggest it will work?**
- Does it work? **Are there key surrogate biomarkers for human diseases to test.**
- For which diseases and conditions does it work? **What is the correct dose** of the supplement and how long must it be given to see an effect?
- Is it safe? **Does it have a long history of use in humans?** What are the side effects? Are there situations in which it might be harmful?
- How should it be given?
- Are there certain sub groups of patients for which it works better?
- Can it be used safely with other forms of treatment?

Development of a Clinically Proven,
Mechanistically Based Medical Food
(A Case Study of a Gammalinolenic
Acid/ Eicosapentaenoic Acid
Combination)

Overview of Clinical Trials with Our GLA/EPA Combination

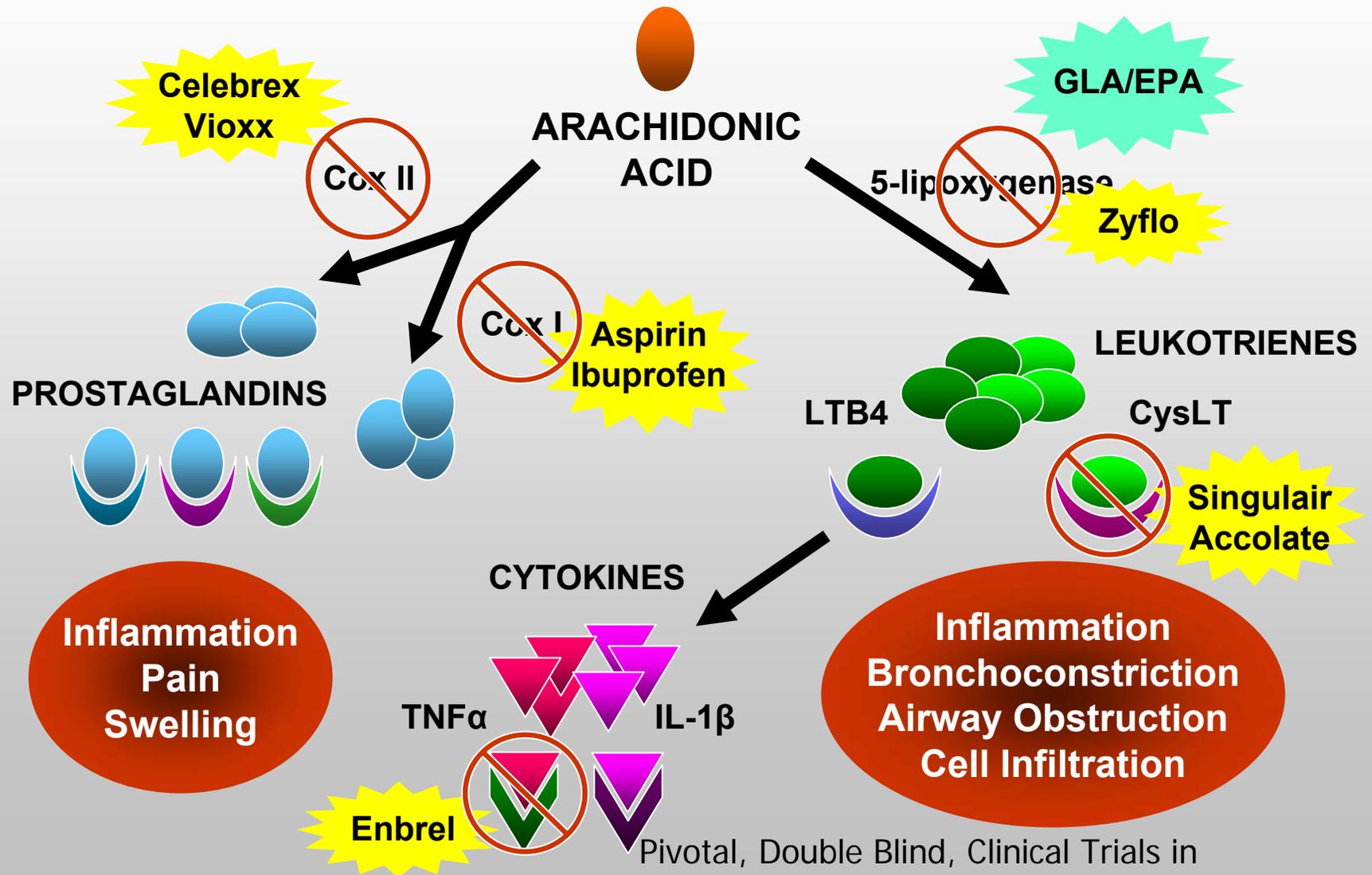
- A proof of principle study in the General Clinical Research Center at Wake Forest University School of Medicine
- An optimization of dose and active ingredients trial in the General Clinical Research Center at Wake Forest University School of Medicine
- A trial to optimize the bioavailability, safety and efficacy of the active ingredients in Airozin™ at the Quintiles Phase I Clinical Trials Center in Lenexa, Kansas
- A Phase II efficacy trial in asthmatics in the General Clinical Research Center at Wake Forest University School of Medicine
- A multi-center pediatric pharmacokinetics trial completed by CompleWare Corporation, Iowa City, Iowa
- Analysis of responders and non-responders

Results have led to seven peer-reviewed journal articles and patents covering this GLA/EPA combination for numerous inflammatory disorders, its formulations, and bioavailability

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Theoretical: The Arachidonic Acid Pathway: Precedent for Safe and Profitable Intervention



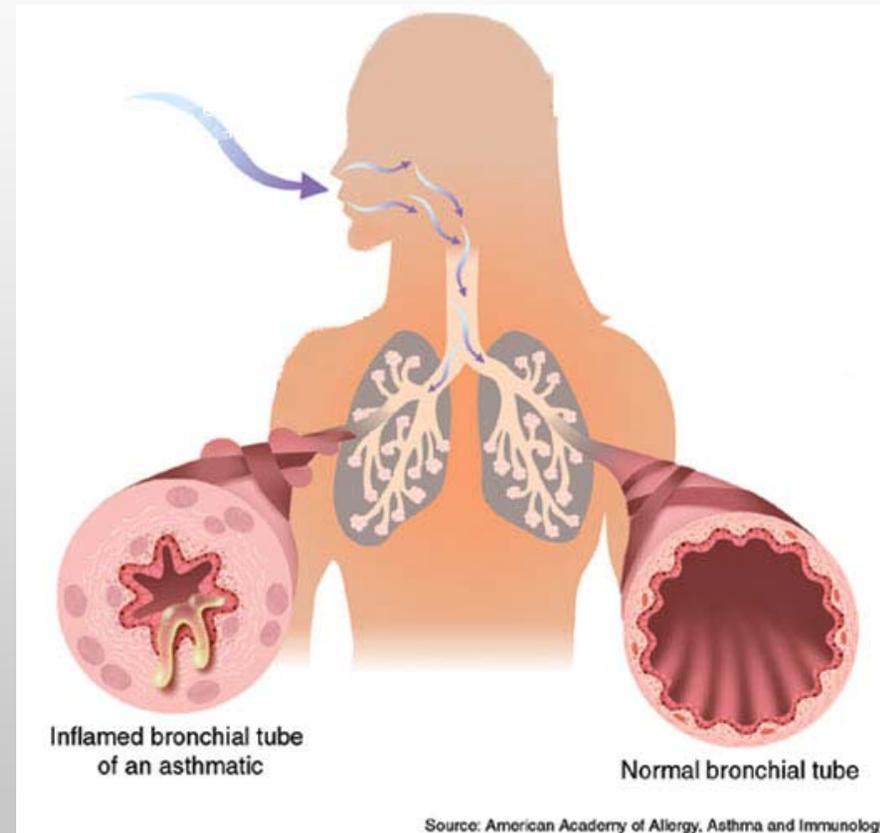
Pivotal, Double Blind, Clinical Trials in Arthritis and ARDS by Zurier and Gadek and colleagues

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Leukotriene Blockers are Proven for Asthma Management

- US incidence - 26.7 million in 2002*
- US incidence has doubled over the last 20 years**
- Asthma is a profound inflammation of airways
- Anti-inflammatory drugs, steroids and leukotriene blockers, are proven to be the most successful therapy
- Leukotriene blockers are a rapidly growing class of drugs, exemplified by Merck's Singulair® with 2003 projected sales of \$2.2 billion up from \$1.0 billion in 2000***

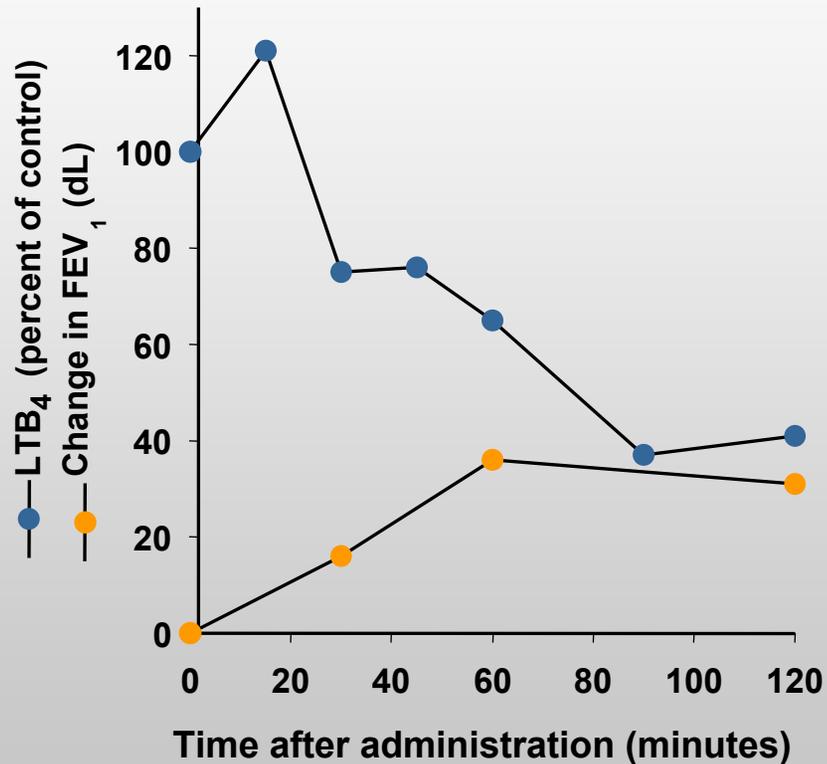


* Center for Disease Control

** American Academy of Allergy and Immunology

*** Morgan Stanley research (1/28/03)

Blood LTB₄ Levels on Pulmonary Function

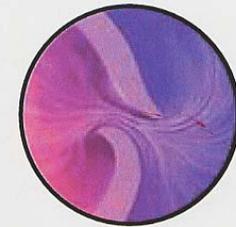


Adapted from: Israel et al., *Annals of Internal Medicine* 119:1059
Rubin et al., *Agents and Actions (Suppl.)* 35:103

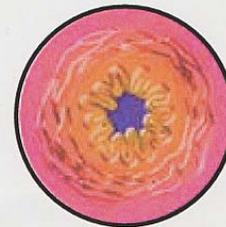
Signs of airway inflammation include



Recruitment of inflammatory cells (neutrophils/eosinophils) to lungs



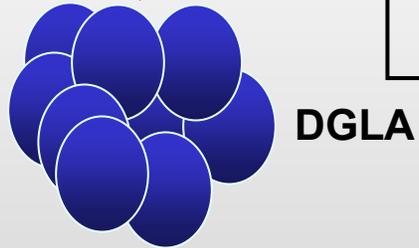
Airway edema



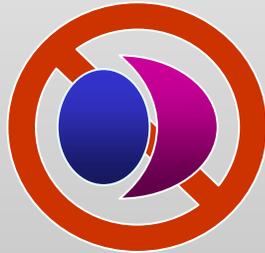
Bronchial constriction



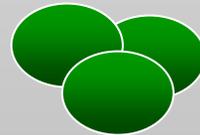
Inflammatory reaction



GLA inhibition of
5-lipoxygenase and reduction
of leukotrienes



5 - lipoxygenase



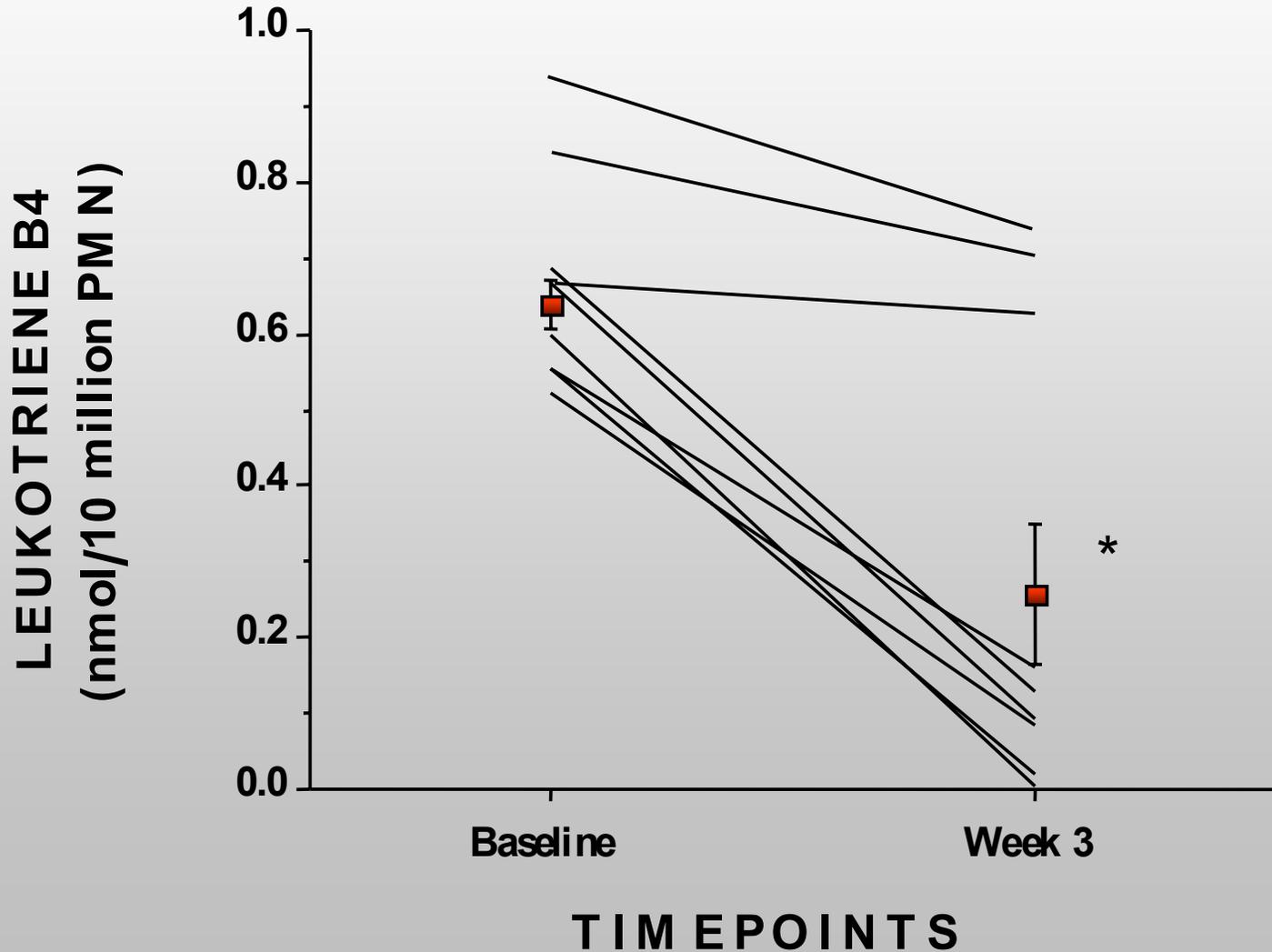
LEUKOTRIENES



ARACHIDONIC
ACID

Asthma
Symptoms

Effect of GLA supplementation on Leukotriene Generation (J.Nutr.127:1435)

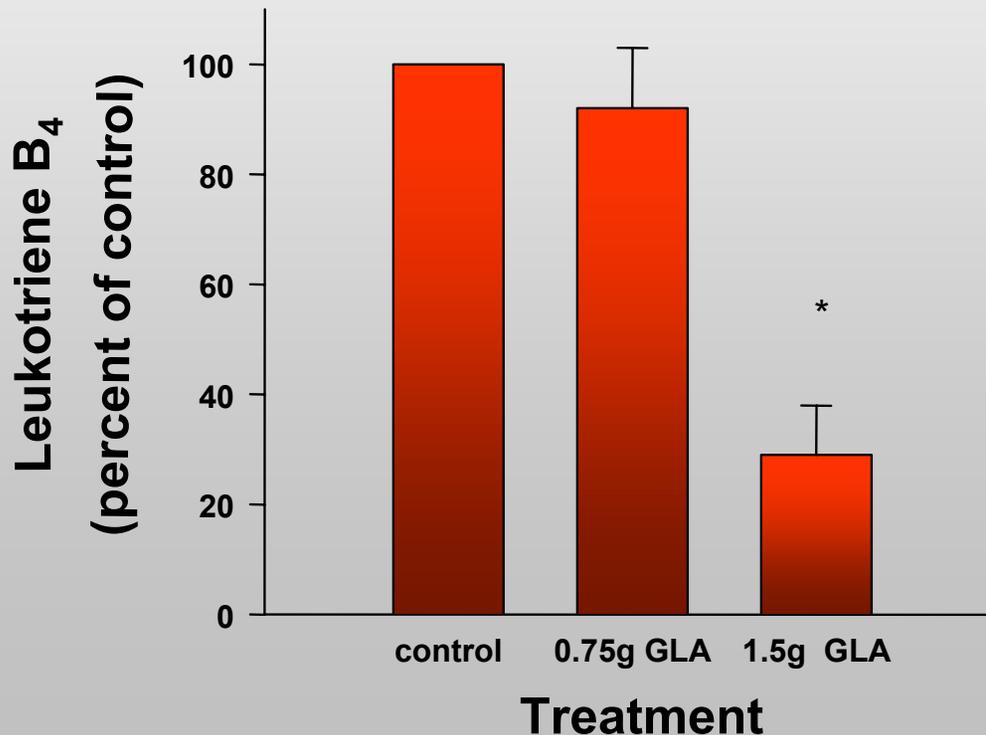


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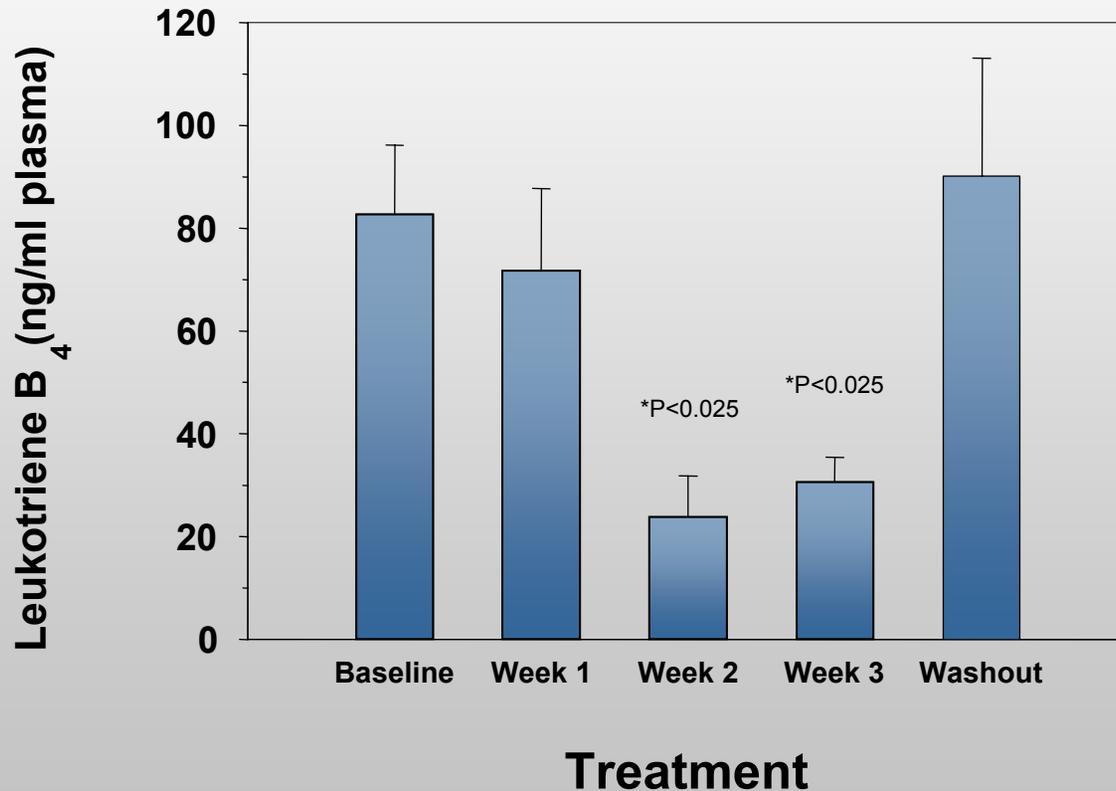
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Dose-dependence of dietary GLA for the inhibition of leukotriene synthesis in zymosan-stimulated blood leukocytes.

*significantly different from control



This GLA/EPA Combination Blocked Leukotrienes in a Time Dependent Manner

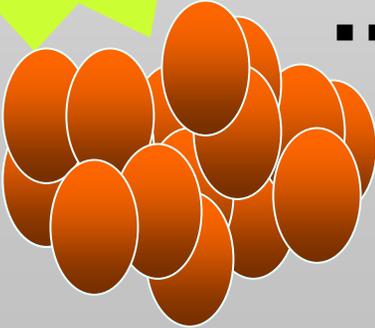
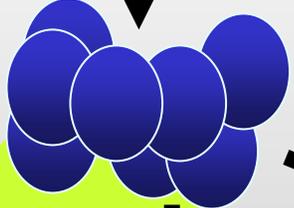
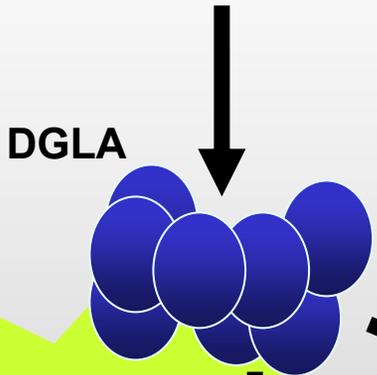


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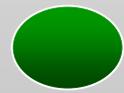
GLA as a mono-therapy increased liver arachidonic acid levels because $\Delta 5$ desaturase is present



ARACHIDONIC ACID

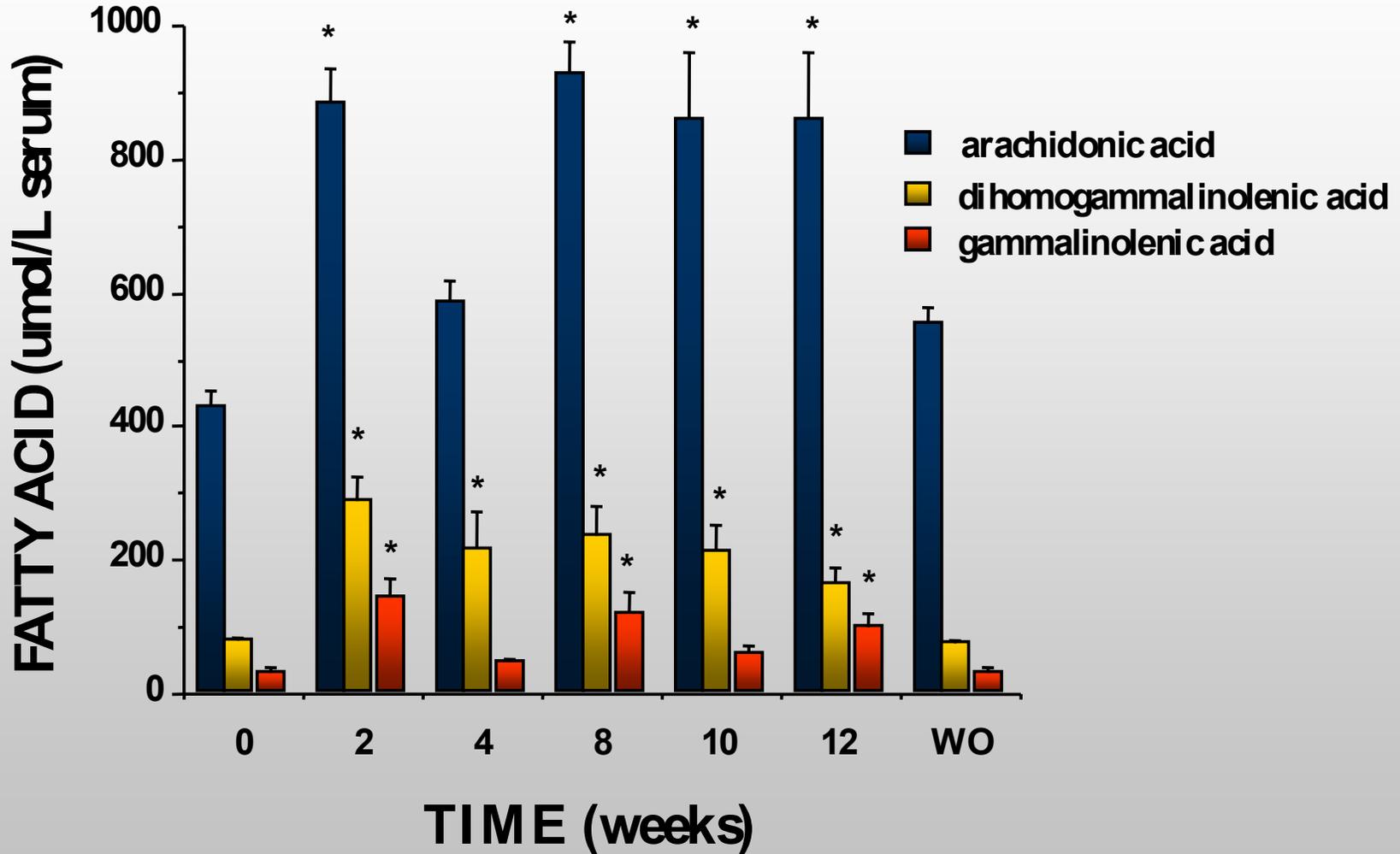


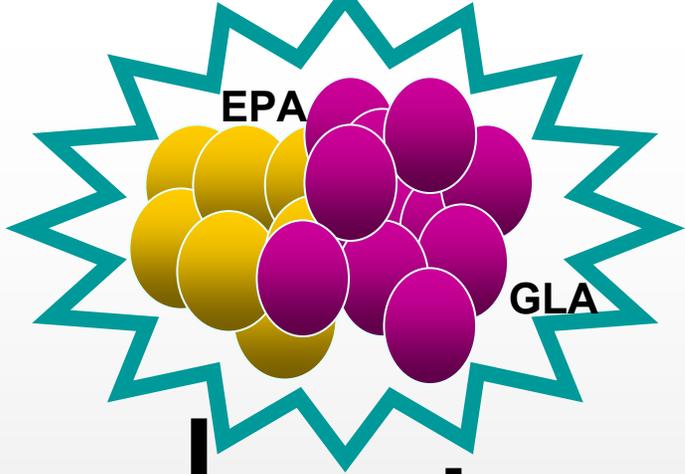
5 - lipoxygenase



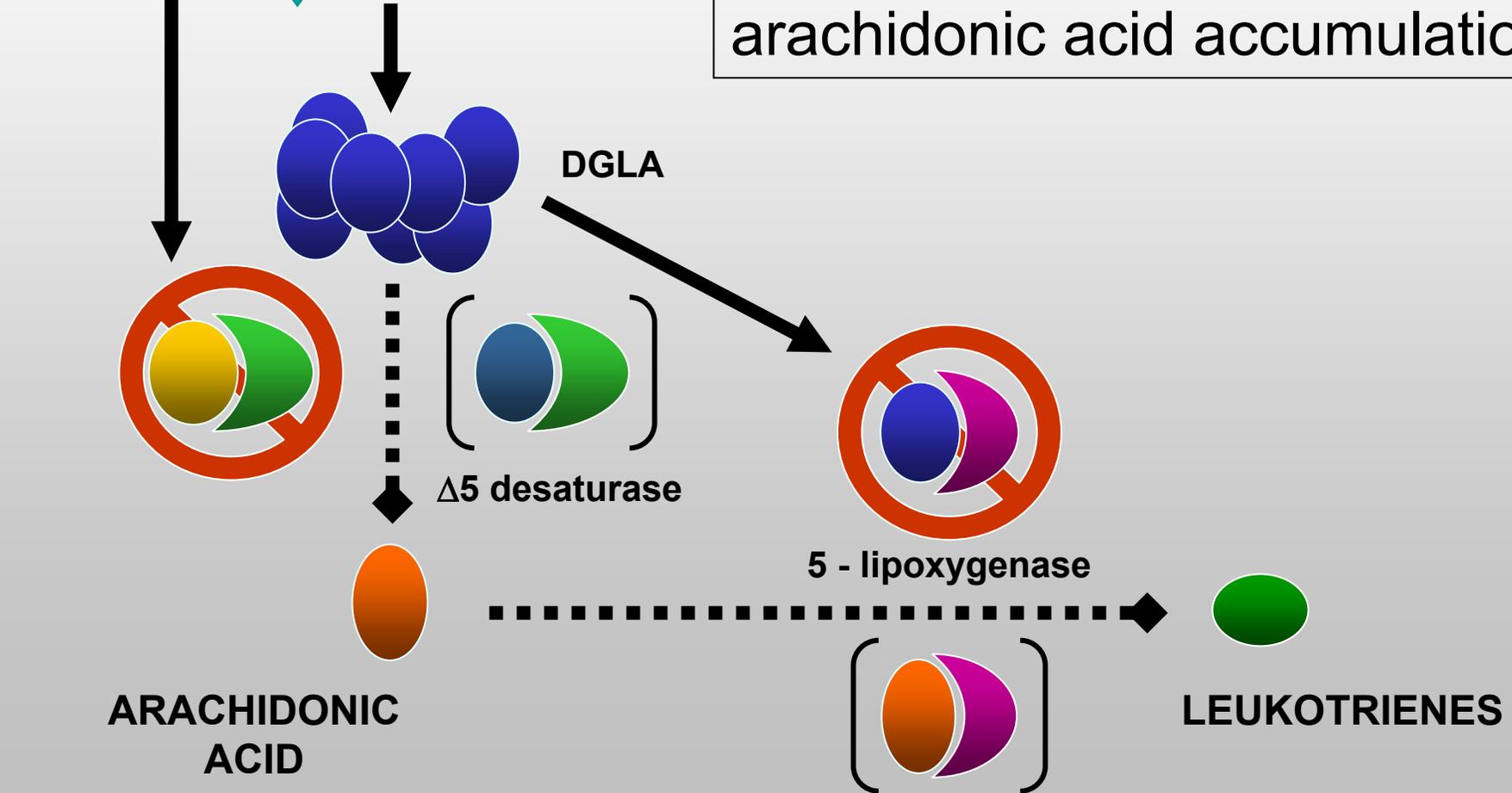
LEUKOTRIENES

Effect of GLA Supplementation on Serum Fatty Acid Concentrations (J.Nutr.127:1435)

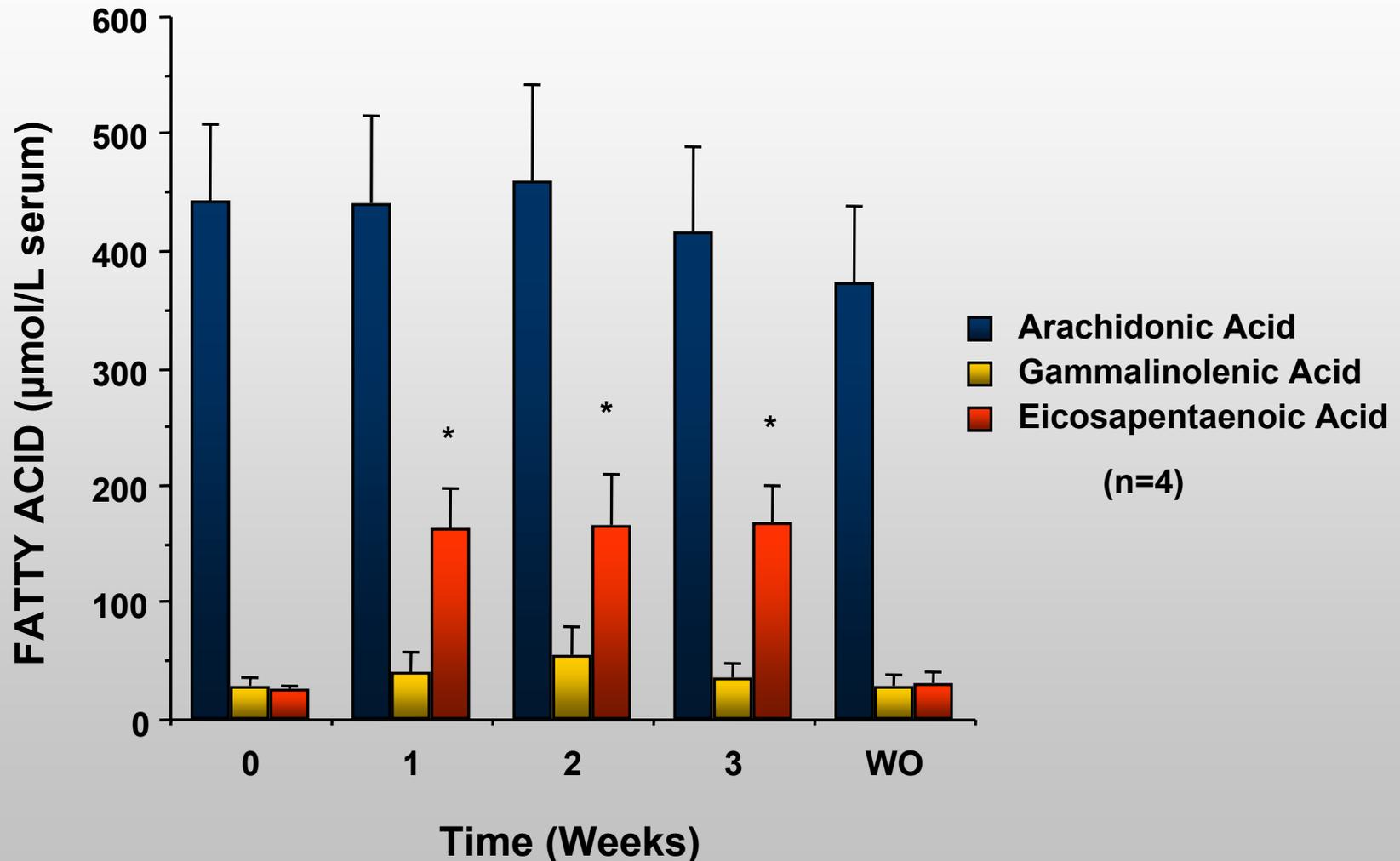




Precise concentrations and ratios of GLA and EPA were developed that reduced leukotrienes and avoided arachidonic acid accumulation



Effects of a GLA and EPA Combination on Serum Concentrations of Fatty Acids



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Gel Capsules Required to Get the GLA and EPA Doses Needed to Inhibit Leukotrienes

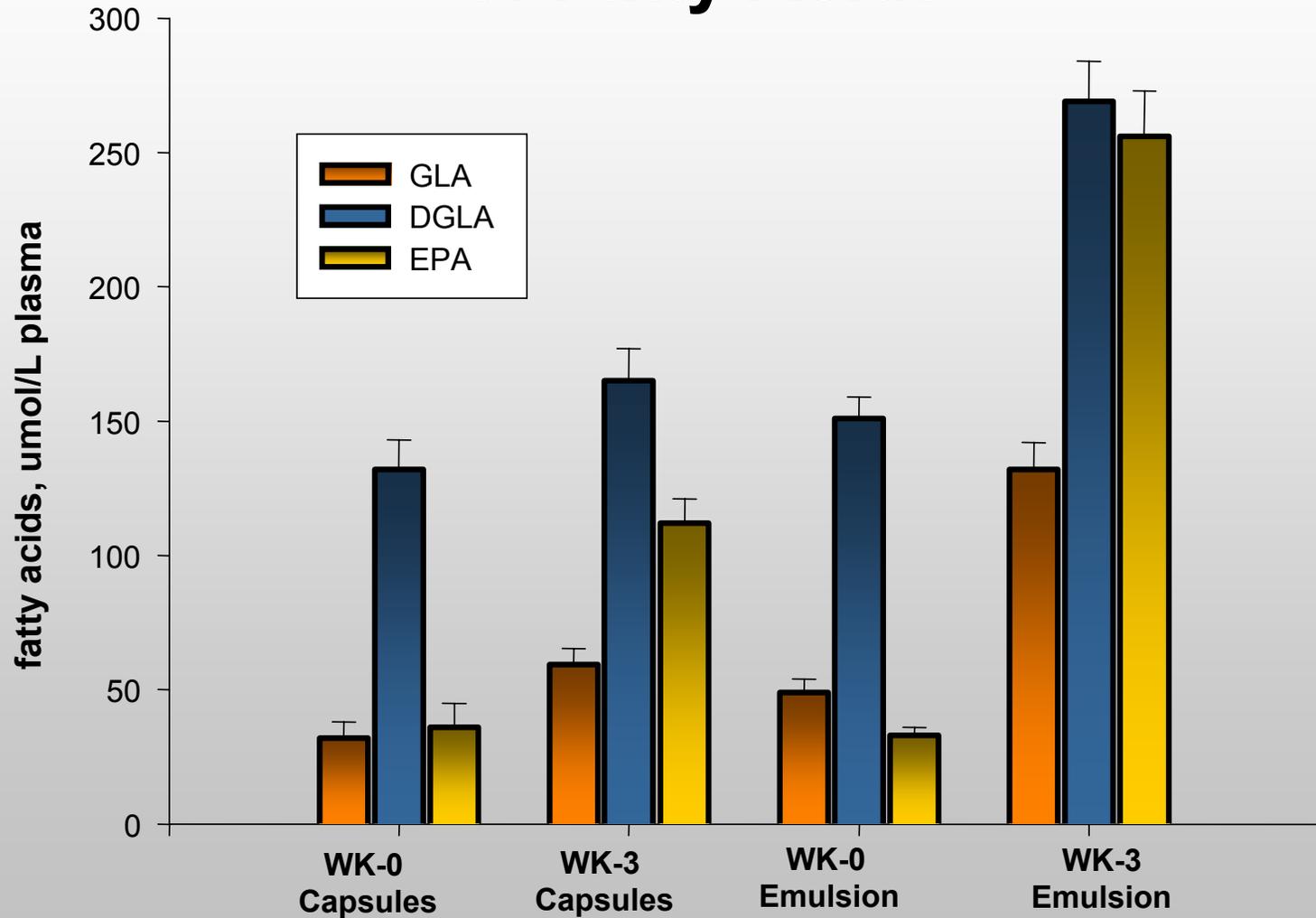
GLA
capsules



EPA
capsules



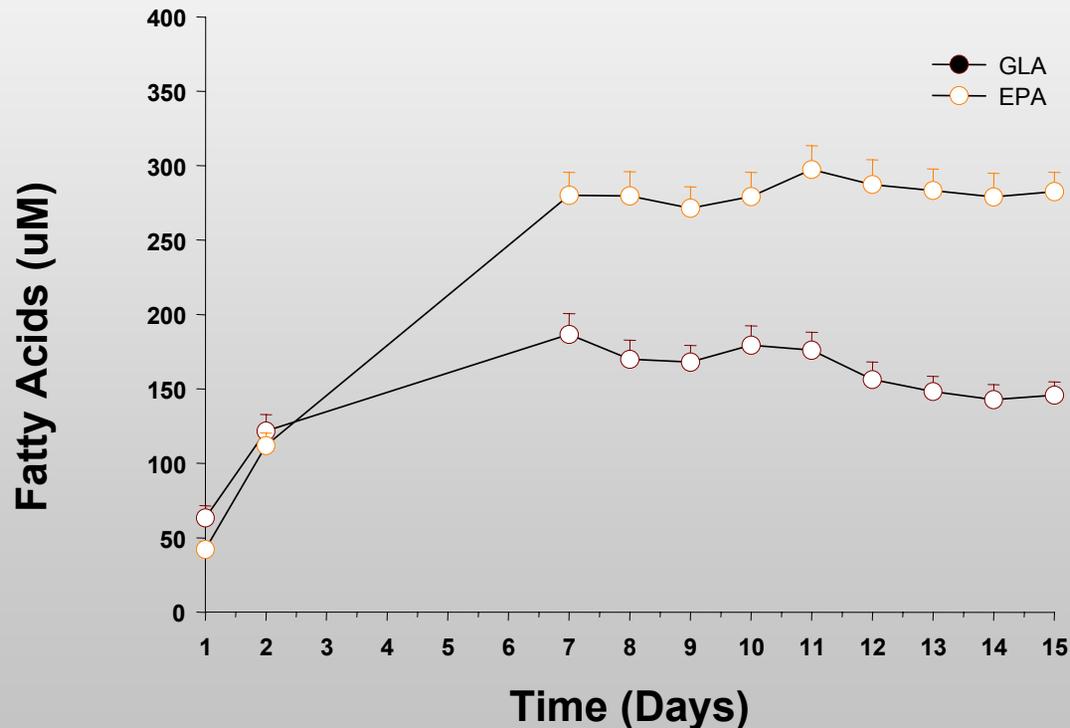
Optimizing the Oral Bioavailability of Fatty Acids



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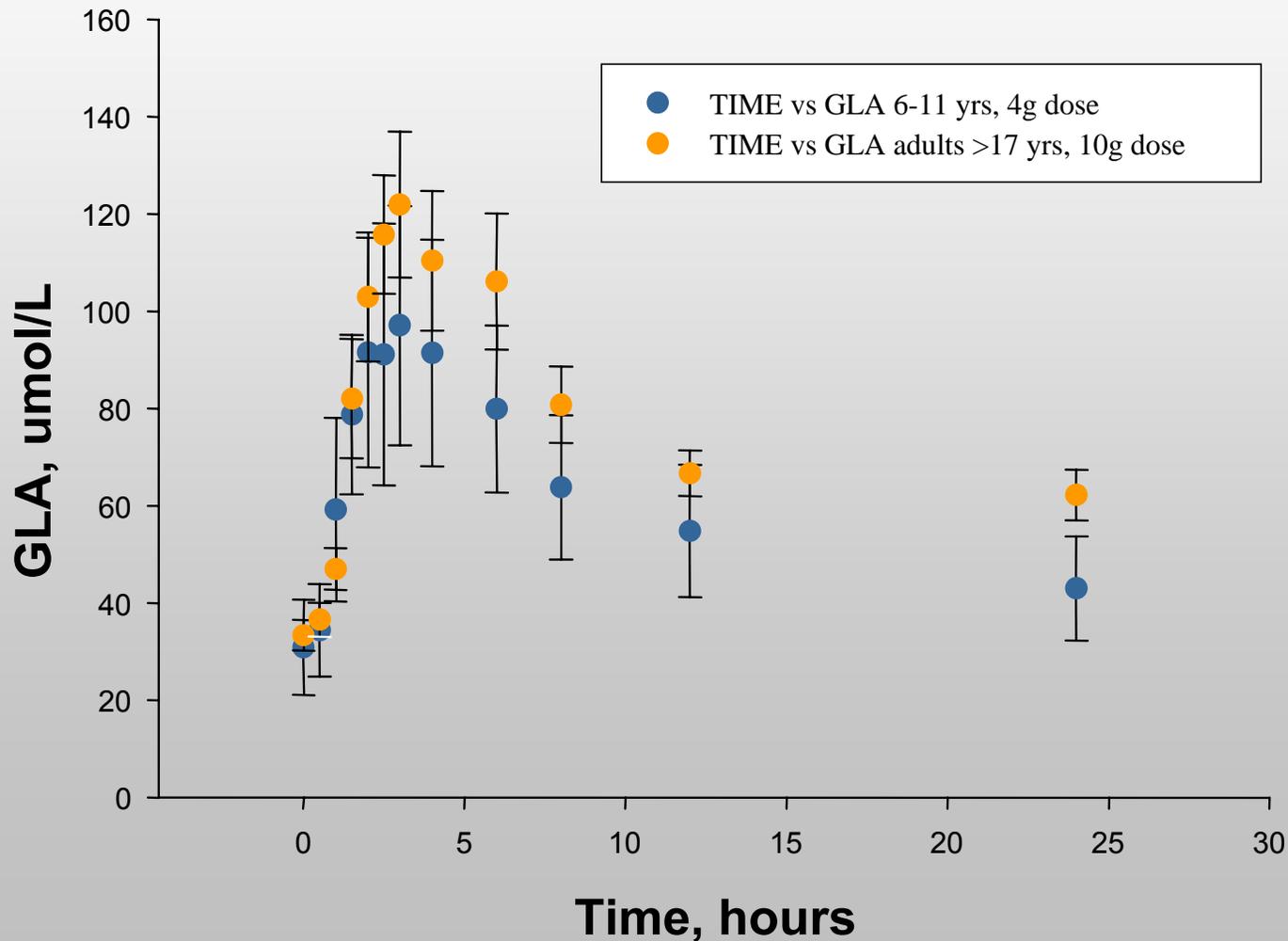
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Trough plasma GLA and EPA concentrations in subjects consuming the 1.8g/day of GLA and 0.9g/day of EPA

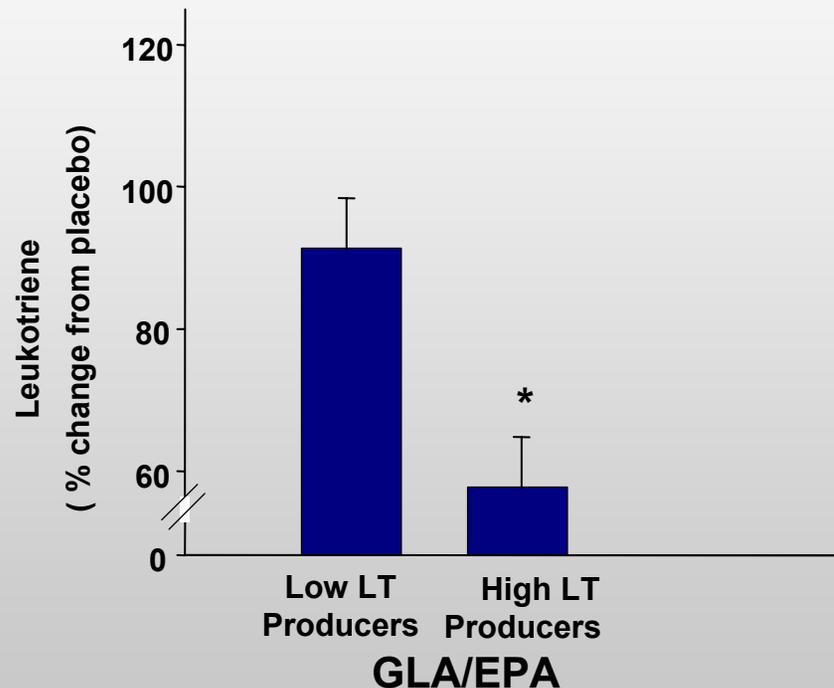


Surette ME, Koumenis I, Edens M, Tramposch KM and Chilton FH. Clin. Therapeutics 25: 972-979, 2003.

Pharmacokinetics in Children and Adults



Comparison of Leukotriene Inhibition Observed in Responder and non-Responder Asthmatics with GLA/EPA



Surette ME, Koumenis I, Edens M, Tramposch KM and Chilton FH. Clin. Therapeutics 25: 948-971, 2003

Can We Reduce the Cost and
Time that It Takes to Develop an
Ethical, Natural Product? |
Believe the Answer is Yes.

Acknowledgments:

NIH/NCCAM/Office of Dietary
Supplements-Wake Forest and
Brigham and Women's Center for
Botanical Lipids